REMARKS

Claims 36, 41-43, 57, 59, 60, and 89-97 are pending. Claims 89-91 were rejected under 35 U.S.C. § 112, first paragraph, and claims 36, 41-43, 57, 59, 60, and 92-97 were rejected under 35 U.S.C. § 103. Applicant addresses each of these rejections as follows.

Claim amendments

Applicant has amended claim 36 to recite that the class I antigen on the cell or tissue in the transplantable composition is masked by a non-complement fixing antibody which lacks the Fc portion. In view of the amendment to claim 36, claims 41-43 have also been amended. Support for these amendments may be found, for example, at page 4, line 27, to page 5, line 4, page 8, lines 15-19, page 12, lines 26-32, and page 13, line 14, to page 18, line 16, of the specification. No new matter has been added by these amendments.

In addition, Applicant notes that claim 42 submitted in a Preliminary Amendment filed with the present application on September 9, 1997 depended from claim 36 and recited that the "masking agents are obtained from polyclonal antisera raised against the antigen." Claim 42 was examined in the present application, and the limitations presently added to claim 36 fall within the scope of claim 42 as filed with the application. Applicant submits that the present amendments do not require a new search.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 89-91 were rejected under 35 U.S.C. § 112, first paragraph, on the assertion that the specification fails to (1) enable the invention, (2) provide adequate written description for the invention, and (3) set forth the best mode for carrying out the claimed invention. Applicant, without agreeing with the Office, and solely to expedite prosecution, has canceled claims 89-91. This rejection, therefore, is moot.

Rejection under 35 U.S.C. § 103

Claims 36, 41-43, 57, 59, 60, and 92-97 were rejected under 35 U.S.C. § 103(a) as being obvious over Stock et al. (Journal of Surgical Research 46:317-321, 1989; "Stock"). In particular, the Office stated (page 3):

> Applicants argue that their results could not have been predicted by Stock et al., and Stock et al. carried out *in vitro* experiments. As argued, it could not have been predicted that instant $F(ab)_2$ masking would allow successful, long term transplantation of foreign tissue into a living animal without humoral immune system-mediated rejection.
> The Examiner notes that the claims are not limited to that which is argued.
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> Applicants argue that Stock et al. employed intact antibodies, which cannot be used *in vivo* since the Fc portion would fix complement. The examiner contends that the instant claims do not exclude intact antibodies.

Claims 59, 60, and 94-97 have been canceled and the rejection of these claims is moot. Applicant submits that the present claims are free of the § 103 rejection.

As noted above, the claims have been amended to recite that the class I antigen on the cell or tissue in the transplantable composition is masked by a non-complement fixing antibody lacking the Fc portion to decrease the immune response such that, upon introduction of the composition into a human, lysis of the cell or tissue is prevented. Clearly, the claims require that lysis of the transplantable composition is prevented *in vivo*. This invention is non-obvious over Stock.

Stock describes *in vitro* experiments in which murine pancreatic islet cells were treated with intact anti-class I murine monoclonal antibody and then incubated with murine T-lymphocytes. In addition, Stock reports, under "Results" on page 319, that "generation of allospecific CTL [cytotoxic T-lymphocytes] was nearly abrogated by anti-MHC class I pretreatment" and goes on to suggest, in the last paragraph on page 320, that a "possibility [for preventing rejection] could involve blocking the MHC class I signal with an $F(ab)_2$ fragment of the appropriate anti-MHC class I antibody." These teachings do not render the presently claimed invention obvious.

First, Applicant's discovery that islet cells of one species masked with a non-complement fixing antibody fragment (e.g., a $F(ab')_2$ fragment) could be successfully transplanted into an animal of a different, unrelated species without rejection, and with long-term maintenance of function, was totally unexpected and could not have been predicted from Stock or any other prior art. Applicant's claims, which require masking an HLA class I antigen on a cell or tissue with non-complement fixing antibodies lacking

the Fc portion, thereby preventing lysis of a transplanted cell or tissue *in vivo*, reflect this discovery.

Second, Stock carried out *in vitro* experiments, which, as is well known, frequently fail to be predictive of *in vivo* results. The present claims require that the antigen on the cell or tissue of the transplantable composition is masked to decrease the immune response, such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented. Thus, the claims require *in vivo* protection from lysis of the transplantable composition. Nothing in the Stock *in vitro* experiments takes into account the humoral immune response known to play a major role in the rejection of transplanted tissue *in vivo*.

In fact, before Applicant carried out her experiments, it could not have been predicted that masking using a non-complement fixing antibody lacking an Fc portion would allow successful, long-term transplantation of foreign tissue into a living animal without humoral immune system-mediated rejection. Applicant found that the $F(ab')_2$-pretreated transplanted tissue was essentially free of adjacent lymphocyte deposits 200 days following transplantation, and further found that the transplanted cells were functional after 200 days. Certainly nothing in Stock was predictive of this dramatic result.

Further, based on the results of the Stock experiments, one of ordinary skill in the art would not have expected masking to succeed by using antibodies lacking the Fc

portion. Stock used intact antibodies, which cannot be used *in vivo* because the Fc portion would fix complement and bring about lysis of the transplant. If one were to have addressed this problem by substituting antibodies lacking the Fc portion, such as $F(ab')_2$ fragments, for intact antibody molecules, one would have expected to compound the potential problem of antibody dissociating from the transplant, exposing the previously masked antigens to the host's T-lymphocytes. As Applicant set forth in the last reply, $F(ab')_2$ fragments have notoriously low affinities for cell surface antigens, compared to intact antibodies. Thus the long-term success obtained by Applicant was all the more surprising, as it employed $F(ab)_2$ fragments.

In sum, there could have been no reasonable basis for predicting, based on the Stock *in vitro* experiments using murine cells, that Applicant could successfully implant tissue into a human, and that this tissue would not be lysed *in vivo*. The present claims are directed to this discovery and the § 103 rejection should be withdrawn.

CONCLUSION

Applicant submits that the application is now in condition for allowance and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office Action for three months, to and including March 10, 2004, and a check in payment of the required extension fee. In addition, Applicant encloses a Notice of Appeal. In this Notice, Applicant respectfully appeals to the Board of Patent Appeals and Interferences from the decision dated September 10, 2003, in which the Office finally rejected claims 36, 41-43, 57, 59, 60, and 89-97 of the above-captioned patent application.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 10, 2004

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